Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol / Caffeine 500mg/65mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg and Caffeine 65mg
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule shaped tablets
White to off white, capsule shaped, biconvex tablets plain on both sides approximately 17.46mm x 7.14mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 16 years or over.

4.2 Posology and method of administration

Posology
Adults (16 years and over):
Two tablets up to four times daily. The dose should not be repeated more frequently than every 4 hours. Do not exceed 8 tablets in 24 hours.

Elderly:
As for adults.

Not recommended for children under 16 years.

The lowest dose necessary to achieve efficacy should be used.
Should not be used with other paracetamol-containing products.

Renal Impairment:
Patients who have been diagnosed with renal impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol and caffeine products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug.

In case of renal insufficiency dose adjustment is necessary:

Hepatic Impairment:
Patients who have been diagnosed with liver impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol and caffeine products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug.

In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged. The daily effective dose of paracetamol should not exceed 60 mg/kg/day (up to maximum 2 g paracetamol /day) in the following situations:

- Adults or adolescents weighing less than 50 kg

- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-heamolytic jaundice)
- Dehydration
- Chronic malnutrition

- Chronic alcoholism

Method of administration
Route of administration: Oral

4.3 Contraindications

Hypersensitivity to paracetamol, caffeine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs, sepsis and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9). In patients with glutathione depleted states such as sepsis; the use of paracetamol may increase the risk of metabolic acidosis.

Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatoxicity which may warrant dosage adjustment.

Underlying liver disease increases the risk of paracetamol related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Alcohol should not be used during the treatment with paracetamol.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such cases.

Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.

Paracetamol & Caffeine 500mg/65mg Tablets should be given with care to patients with gout, hyperthyroidism and arrhythmia.

The patient should limit the use of caffeine containing products when taking Paracetamol & Caffeine 500mg/65mg Tablets, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heart beat.

Glomerular filtration Dose
10-50 ml/min 1 tablet every 6 hours
< 10 ml/min 1 tablet every 8 hours

As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 390 mg/day of caffeine (6 tablets) per day. Patients should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose.

Typical amounts of caffeine available from dietary sources are
Brewed coffee; 50-100mg/100ml*
Instant coffee and tea: 20-73mg/100ml*
Carbonated drinks (cola) 9-19mg/100ml*
Chocolate 5-20mg/100ml
(*100ml is equivalent to about 1 small cup of fluid)

Prolonged use except under medical supervision may be harmful. In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a doctor or dentist and not at high doses.

The stated dose must not be exceeded. Paracetamol & Caffeine 500mg/65mg Tablets should be taken only when necessary. If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Important information regarding the ingredients of this medicine
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

Probenecid causes an almost two-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination half-life of Paracetamol.

The absorption of paracetamol may be increased by metoclopramide and decreased by colestyramine.

Oral contraceptives may increase the rate of clearance of paracetamol.

Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Isoniazid reduces paracetamol clearance by 20%, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver. The clinical relevance is unknown.

Paracetamol decreases the bioavailability of lamotrigine with possible reduction of its effect due to possible induction of its metabolism in the liver.

Co-administration of paracetamol with zidovudine may result in neutopenia or hepatotoxicity. However, these effects have not been consistently reported. The chronic / multiple dose paracetamol use in patients on zidovudine therapy should be avoided, however, if chronic paracetamol and zidovudine are to be given concurrently white blood count and liver function tests should be monitored particularly in malnourished patients.

Paracetamol may increase the elimination half-life of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

Flucloxacillin: Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

Caffeine

Phenylpropanolamine increases caffeine plasma concentrations four-fold. There is a risk of additive CNS adverse events. Isolated reports describe the development of acute psychosis when caffeine was given with phenylpropanolamine.

Fluvoxamine, a potent inhibitor of CYP 1 A2, markedly reduces the clearance of caffeine. Concomitant administration may lead to caffeine intoxication.

Ciprofloxacin reduces caffeine metabolism, leading to two-fold increases in caffeine plasma concentrations.

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers. Caffeine may enhance the tachycardic effect of phenylpropanolamine and other sympathomimetic drugs.

Caffeine can increase blood pressure and counters the hypotensive action of Beta blockers such as atenolol, metoprolol, oxprenolol and propranolol. This medicine should not be used at the same time as beta blockers.

Disulfiram decreases caffeine clearance by up to 50%. Concomitant use of disulfiram and Paracetamol & Caffeine 500mg/65mg Tablets should be avoided.

Dipyridamole: injectable dipyramidole: decrease of the vasodilating effect of dipyramidole.

Treatment with caffeine should be discontinued at least 5 days before myocardial imaging. Coffee, tea and chocolate consumption should be avoided in the 24 hours preceding the test. Use with caution.

Enoxacin: increase of caffeine plasmatic concentrations due to a decrease of its hepatic metabolism, which can lead to excitement or hallucinations. Concomitant use is therefore not recommended.

Mexiletine: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with mexiletine. To be taken into account.

Norfloxacin: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with norfloxacin. To be taken into account.

Stiripentol: possible increase of caffeine plasmatic concentration with risk of overdose, due to its hepatic metabolism inhibition. Use with caution.

Caffeine exerts a competitive inhibition of the metabolism of clozapine. Therefore clozapine and caffeine must not be used concurrently.
Caffeine can increase the elimination of lithium from the body. Concomitant use is therefore not recommended.

Monoamine oxidase inhibitors may increase the stimulant effects of caffeine.

Methoxsalen reduces clearance of caffeine and may increase the effects of caffeine.

Phenytoin doubles caffeine clearance, although caffeine does not affect the metabolism of phenytoin.

Pipemidic acid reduces caffeine clearance, enhancing the effects of caffeine.

Theophylline and caffeine share the same metabolic pathway, leading to decreased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided.

Levothyroxine, like caffeine can increase blood pressure, and therefore these two active ingredients should not be used concurrently.

Ephedrine and caffeine interact to produce significant cardiovascular effects. Therefore caffeine should be avoided when ephedrine is being taken.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Paracetamol-caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.
Caffeine in breast milk may have a stimulating effect on breast-fed infants. Irritability and poor sleeping pattern in the infant have been reported.

Not recommended for use during breastfeeding.

Fertility
There is insufficient information available on the effects of Paracetamol and Caffeine on human fertility.

4.7 Effects on ability to drive and use machines

Paracetamol / Caffeine 500mg/65mg Tablets has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from minimal patient exposure. Accordingly, adverse events reported from extensive post-marketing experience at therapeutic/labelled dose are listed below by system organ class and frequency.

Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000 including isolated reports) and not known (cannot be estimated from available data).

Frequency	System	Symptoms
Common >1/100, <1/10	Psychiatric disorders:	Insomnia, restlessness, anxiety
	Gastrointestinal disorders	Gastrointestinal disorder
Rare >1/10000 - < 1/1000	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders.
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS,
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
	Hepato-biliary disorders	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria
	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (< 10 000)	Hepato-biliary disorders	Hepatotoxicity, hepatic dysfunction
	Blood and lymphatic system disorders	thrombocytopenia leukopenia neutropenia

		hemolytic anemia agranulocytosis
	Immune systemdisorders	Anaphylaxis,Cutaneous hypersensitivity reactions, Angioedema, Stevens Johnson Syndrome andtoxic epidermal necrolysis
	Metabolism and nutrition disorders	Hypoglycaemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects
	Respiratory, thorasic and mediastinal disorder	Bronchospasm inpatients sensitive to aspirin and other NSAIDs
	Skin and subcutaneous disorders	Serious skin reactions have been reported.

Not known: Irritability, Palpitations, tachycardia, Edema of the larynx, anaphylactic shock, anaemia, , liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), **gastrointestinal effects** and vertigo have been reported.

Undesirable effects associated with caffeine component

System	Undesirable Effect	Frequency
Central Nervous system	Nervousness, Dizziness	Not known
Cardaic disorders	Palpitations	Not known
Psychiatric disorders	Insomnia, restelessness, anxity and irritability	Not known
Gastrointestinal disorders	Gastrointestinal disturbances	Not known

When the recommended dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as nervousness, dizziness, insomnia, restlessness, anxiety, irritability, headache, gastrointestinal disorder and palpitations.

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance website: www.hpra.ie

4.9 Overdose

Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity. Risk Factors include: If the patient;
- Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Regularly consumes ethanol in excess of recommended amounts
- Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Emergency Procedure: Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion.
Administration of activated charcoal should be considered if >150mg/kg paracetamol has been taken within 1 hour.
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines
Symptomatic treatment should be implemented.
Administration of activated charcoal should be considered if >150mg/kg paracetamol has been taken within 1 hour.
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines
Symptomatic treatment should be implemented.

Caffeine
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).
It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity. No specific antidote is available, but supportive measures such as beta adrenceptor antagonists to reverse the cardiotoxic effects may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Analgesics; Other Analgesics and Antipyretics; Analides: Paracetamol, combinations excl.
ATC code: N02B E51

The combination of paracetamol and caffeine is a well-established analgesic combination.

Paracetamol
ANALGESIC:
The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

ANTIPYRETIC:
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Caffeine
Central nervous system stimulant – Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amfetamines.

ANALGESIA ADJUNCT:
Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic.

5.2 Pharmacokinetic properties

PARACETAMOL
Absorption and Fate
Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Physiopathological Variations: Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed

CAFFEINE
Absorption and Fate
Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.
Preclinical safety data on paracetamol in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not been mentioned elsewhere in this Summary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K-30 (E1201)
Povidone K-90 (E1201)
Potato starch
Pregelatinised starch
Purified Talc
Croscarmellose sodium
Stearic acid (E570)
Magnesium stearate

6.2 Incompatibilities

Not applicable .

6.3 Shelf life

24 months.

6.4 Special precautions for storage

No special storage conditions

6.5 Nature and contents of container

Paracetamol / Caffeine 500mg/65mg Tablets are packaged in blister packs comprising of white opaque PVC/PVdC (20 micron/40gsm) and with backing of foil, which are placed in an outer carton along with leaflet. These are available in the pack sizes of 4, 6, 12, 16, 24, 30, 32, 48, 60 and 90 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Brillpharma (Ireland) Limited

Inniscarra
Main Street
Rathcoole
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22749/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th December 2014
Date of last renewal: 19th November 2019

10 DATE OF REVISION OF THE TEXT

July 2022